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Acute Myelofibrosis Terminating in Acute Lymphoblastic Leukemia: Case Report and Review of the Literature

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Acute myelofibrosis (AMF), as defined by an acute panmyelopathy associated with marked megakaryocytic hyperplasia and marrow fibrosis, appears to be a stem cell disorder. Even though it is most difficult to distinguish from various myeloproliferative and myelodysplastic disorders as well as acute myelogenous leukemia, it has rarely been reported to terminate as acute lymphoblastic leukemia (ALL). Only five cases have been reported in the literature; two from the pediatric literature and only three from the adult literature. Of the three adult cases, two were defined by light microscopy alone. Among the cases with follow-up (3/5), all died within 2 weeks to 2 months of diagnosis. We report an additional case in an adult; the ALL was defined by morphology, flow cytometric immunophenotyping, and cytogenetic analysis. The interval from diagnosis of AMF to ALL was 3 months. Our patient was treated with standard therapy for ALL, was in complete remission at last follow-up (3 months off maintenance therapy), and represents the only reported case who attained a complete remission. There are too few cases to determine the prognostic significance of termination of AMF in an acute leukemia of lymphoid origin vs. myeloid origin. © 1996 Wiley-Liss, Inc.

Key words: acute myelofibrosis, acute lymphoblastic leukemia, flow cytometry

INTRODUCTION

Acute myelofibrosis (AMF) has been referred to previously as "acute myelosclerosis," "malignant myelosclerosis," and "acute myelodysplasia with myelofibrosis" [1–3]. AMF is defined as an acute panmyelopathy associated with marked megakaryocytic hyperplasia and marrow fibrosis [4]. Patients generally present with pancytopenia of sudden onset. Organomegaly is absent. AMF is a term applicable to rare cases of bone marrow failure that are difficult to diagnose because they exhibit features of acute leukemia, chronic myeloproliferative syndromes, and even myelodysplastic syndromes (MDS). These features include pancytopenia, circulating blasts in some cases, hypercellularity, presence of all three lineages, fibrosis, and increased abnormal megakaryocytes. Marked reticulin fibrosis generally results in an inability to obtain, or difficulty in obtaining, diagnostic bone marrow aspirates [4].

Differential diagnosis may be difficult and includes myelogenous leukemia (AML), myeloproliferative disorders, and MDS. AMF may have an acute onset with circulating blasts, similar to AML, but it is difficult to demonstrate that bone marrow blasts exceed 30%, as a result of either a true number less than 30% or obscuration by fibrosis. In addition, in AMF, cells of all three lineages are usually present, prompting use of the imprecise term "panmyelopathy," further decreasing the similarity to acute leukemia. However, differentiation of AMF from AML-M7 can be quite difficult; both are morphologically characterized by megakaryocytic hyperplasia/dysplasia and fibrosis, with or without myelodysplastic changes. In fact, AMF and AML-M7 may be synonymous [1]. It has been postulated that AMF is a hemopoietic stem cell disorder, with AML-M7 representing one subset [5]. Rare cases of AML-M6 with myelofibrosis can also be difficult to differentiate from AMF; both are characterized by myelofibrosis and myelodysplastic changes. AML-M6 is

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characterized by a prominent (greater than 50%) erythroid component, whereas AMF, in general, has a more prominent megakaryocytic component.

Cases of known myeloproliferative disorders may transform to an end stage resembling AMF, and even cases with cytogenetic evidence of a myeloproliferative disorder may present de novo with similarity to AMF. Agnogenic myeloid metaplasia (AMM) in acute transformation can be difficult to distinguish from AMF; however, AMM is associated with splenomegaly, which is not present in AMF.

AMF can also be difficult to distinguish from MDS with extensive fibrosis (MDS-F). Up to 10% of cases of MDS present with extensive fibrosis [6,7]. However, splenomegaly occurs in 40% of cases of MDS-F and is absent in AMF [8]. In addition, the predominance of dyserythropoiesis and the presence of granulocytic hypogranulosis and Pelger-Huet forms in MDS may help to distinguish between these entities, although this distinction may not always be clear. In fact, erythroid hypoplasia was noted in MDS-F by Pagliuca et al. [6], and there is no specific pattern of cytogenetic abnormality in MDS with extensive fibrosis [8]. However, MDS is characterized by a fulminant course and a comparatively longer survival than AMF [6,8].

AMF is known to progress to various types of AML and chronic myelogenous leukemia (CML). Rarely, AMF has been described in association with acute lymphoblastic leukemia (ALL), supporting a possible hemopoietic stem cell origin [9–11]. Amjad et al. [10] state that AMF terminating in ALL would imply less toxic chemotherapy and a better prognosis; however, among the cases in the literature with follow-up (3/5), all died within 2 weeks to 2 months of diagnosis. We report a case of adult AMF, which evolved within 3 months to a common acute lymphoblastic leukemia, early pre-B cell origin, defined by morphology, flow cytometric immunophenotyping, and cytogenetic analysis. Here we describe our findings and review the pertinent literature.

CASE REPORT

The patient is a 44-year-old white male who presented to a local hospital with a chief complaint of cough and shortness of breath. Medical history revealed fever, night sweats, and chills over the 2 weeks prior to presentation. There was no previous history of radiotherapy or chemotherapy. Physical examination failed to reveal splenomegaly. A complete blood count (CBC) revealed pancytopenia [white blood cell count (WBC) 2,100/μl with 16% neutrophils, hemoglobin (Hgb) 11.0 g/dl, and platelet count 68,000/μl]. Chest X-ray revealed a left lower lobe infiltrate. The patient was admitted and treated with triple antibiotic therapy (pipracillin, vancomycin, and gentamycin), with only slight improvement of the WBC (2,800/μl). A bone marrow biopsy was performed, and the bone marrow could not be aspirated. Bone marrow touch preparations and core biopsy were interpreted as most consistent with AMF. The patient was discharged.

The patient presented 3 months later to St. Louis University Health Sciences Center with a chief complaint of fever and weakness. CBC revealed pancytopenia (WBC 3,700/μl with 9% neutrophils and 9% blasts, Hgb 8.0 g/dl, and platelet count 12,000/μl). Bone marrow aspiration and biopsy were performed, with specimens analyzed by flow cytometry and for cytogenetic abnormalities. The bone marrow was diagnostic of common ALL, early pre-B type, French American British (FAB) L2 subtype. The patient was treated via phase I Bonn-Munich-Frankfurt (BMF) protocol (prednisone, L-asparaginase, vincristine, and daunorubicin), completed phase II BMF protocol (cyclophosphamide, cytosine arabinoside, and 6-mercaptopurine, with prophylactic cranial irradiation and intrathecal methotrexate), and completed 77 weeks of maintenance therapy (6-mercaptopurine and methotrexate) [12]. The last bone marrow examination performed after completion of the maintenance therapy, revealed no evidence of ALL; however, there was persistent reticulin fibrosis.

MATERIALS AND METHODS

Flow Cytometry

Peripheral blood and a bone marrow aspirate were analyzed on a FACSCAN flow cytometer (Becton-Dickinson, Mountainview, CA) for various antigens using standard techniques and commercially available monoclonal antibodies, including CD3 (Becton-Dickinson, San Jose, CA); CD4 and CD45 (Becton-Dickinson Immunocytochemistry Systems, Mountainview, CA); CD5, CD8, and CD14 (MO_2) (Gen Trak, Wayne, PA); CD10, CD13, CD14 (My4), CD19, CD20, and CD33 (Coulter Immunology, Hialeah, FL); CD24 (Hybritech, Inc., San Diego, CA); CD34 (Gen Trak, Plymouth Meeting, PA); kappa and lambda (Kallestad, Inc., Chaska, MN); and HLA-DR (Ortho Diagnostic Systems, Raritan, NJ). The expected reactivity of these antibodies in peripheral blood is shown in Table I. These expected reactivities were based on flow cytometric analysis of peripheral blood from 10 healthy adult volunteers.

RESULTS

Light Microscopy

Hematoxylin and eosin stains of the bone marrow core biopsy received from a local hospital revealed marked hypercellularity (90% cellularity), with panmyelopathy. The megakaryocytic series was markedly increased in number, with numerous pleomorphic and mononucleated forms. There were increased blasts, representing approxi-

Table I. Results and Expected Reactivity of Monoclonal Antibodies in Monocyte Region

Monoclonal antibody	Patient results		Expected reactivity
	Peripheral blood	Bone marrow	
CD3	9	8	3 ± 10
CD4	14	14	60 ± 40
CD5	5	8	4 ± 12
CD8	3	7	6 ± 10
CD10	59	60	25 ± 14
CD13	33	37	87 ± 24
CD14	16	17	82 ± 12
CD19	86	76	16 ± 32
CD20	15	17	4 ± 6
CD24	68	56	10 ± 18
CD33	18	22	88 ± 14
CD34	66	57	1 ± 4
CD45	99	98	99 ± 2
Kappa	7	Not done	72 ± 28
Lambda	3	Not done	15 ± 40
HLA-DR	92	90	87 ± 20

mately 20% of the total marrow cellularity (Fig. 1A,B). Myeloperoxidase, nonspecific esterase, and periodic acid Schiff (PAS) stains were performed at the local hospital. Myeloperoxidase stain results were reported as a few blasts with positive staining and many blasts, especially large forms, with no staining. PAS stain was staining the large blasts. Reticulin stain revealed a marked degree (3+/4+) of marrow fibrosis (Fig. 2). Mature erythroid cells were increased; however, dyserythropoiesis and ringed sideroblasts were not present. Thus, the bone marrow biopsy was interpreted as showing AMF with lymphoblasts (<30%). ALL could not be diagnosed but, seen in retrospect, was present at an early state.

Review of the bone marrow biopsy performed 3 months later at St. Louis University Health Sciences Center revealed an acute leukemia with sheets of blasts, in areas involving 100% of the marrow cellularity, associated with extensive areas of necrosis and other areas of myelofibrosis. Touch preparations of the bone marrow core biopsy and bone marrow aspirate smear preparations revealed blasts ranging in size from intermediate to large. They

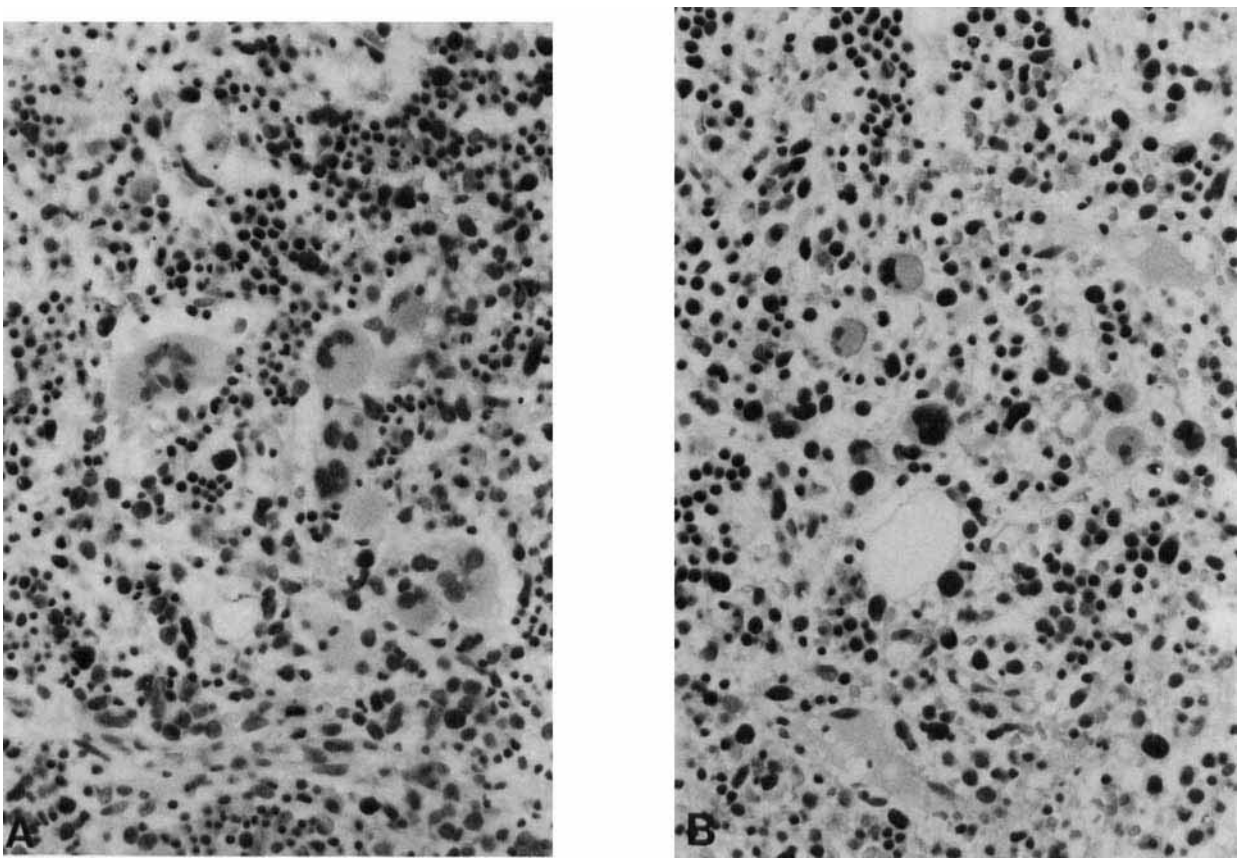

Fig. 1. Initial bone marrow core biopsy demonstrating hypercellularity and megakaryocytic hyperplasia (A) and megakaryocytic dysplasia with increased blasts (B). Hematoxylin-eosin stain, ×400.

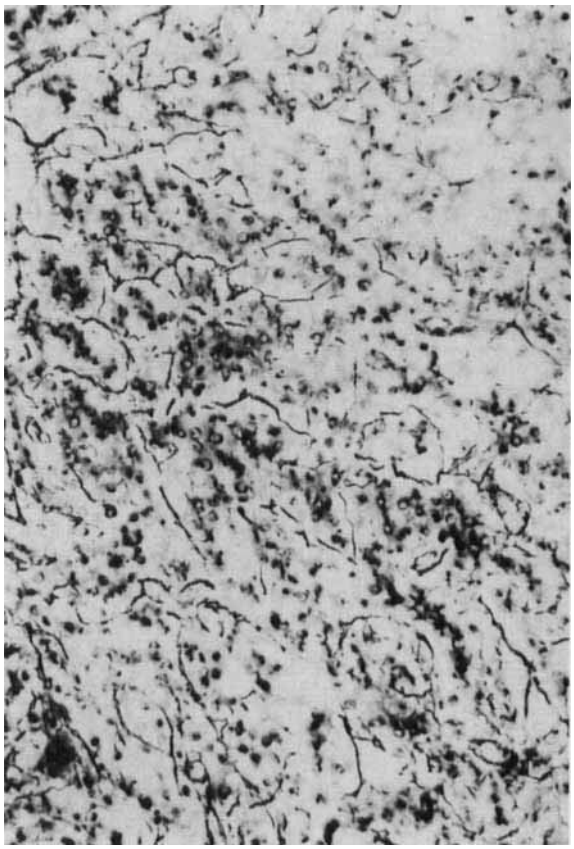

Fig. 2. Initial bone marrow core biopsy, with marked reticulin fibrosis. Reticulin stain, ×400.

were characterized by fine granular chromatin, with prominent nucleoli and varying amounts of dark blue cytoplasm. Because of the difficulty of bone marrow aspiration, adequate material was not obtained for enzyme cytochemical stains or terminal deoxynucleotidyl transferase. The accompanying peripheral blood smear revealed blasts characterized by convoluted nuclei, prominent nucleoli, and deep blue cytoplasm.

Flow Cytometry

Flow cytometric analysis (Table I) of the peripheral blood revealed a decreased WBC of 4,500/μl, with 70% of cells within the lymphocyte region, 17% within the monocyte region, and 13% within the granulocyte region. Cells within the lymphocyte region showed a normal immunophenotype, with 78% T cells, 18% mature B cells, and 2% natural killer cells. Study of cells within the monocyte region showed 68% of cells with an aberrant B-cell immunophenotype ($CD19^+$, $CD24^+$, $CD10^+$, $HLA\text{-}DR^+$, $CD34^+$, $CD20^-$, and sIg^-). CD13 was expressed by 33% of cells in the monocyte region; however, only 3% of cells coexpressed CD19 and CD13. Thus, on flow cytometric analysis, 12% lymphoblasts of an early pre-B immunophenotype with CD34 positivity were identified within the peripheral blood.

Flow cytometric analysis of the bone marrow aspirate revealed a hypocellular specimen (3,200/μl), with 60% of cells within the lymphocyte region, 22% within the monocyte region, and 18% within the granulocyte region. Cells within the lymphocyte region were 85% T cells and 15% mature B cells. Study of cells within the monocyte region showed 60% of cells with an aberrant B-cell immunophenotype as detected in the peripheral blood. Thus, by flow cytometric analysis, 13% lymphoblasts of an early pre-B immunophenotype with CD34 positivity were identified within the bone marrow. The relatively low percentage of blasts within the bone marrow aspirate compared to the core biopsy was most likely due to a difficult aspiration secondary to the myelofibrosis and subsequent hemodilution.

Cytogenetic Analysis

Analysis of 15 cells from unstimulated bone marrow cultures revealed seven cells 46,XY and eight cells 46,XY,del(5)(p15.3), representing a terminal deletion of the short arm of chromosome 5.

DISCUSSION

There are 18 cases described in the literature of AMF associated with AML of varying types (i.e., myelocytic, myelomonocytic). AMF has also been described as evolving into chronic myelogenous leukemia [8]. Of particular interest is the rare termination of AMF in ALL. Two childhood AMFs were described as terminating in ALL of T-cell origin (one case) and null-type (one case) [9,11]. Only three cases have been described in the literature of adult AMF terminating in ALL, defined by light microscopy alone in two [5,10].

We report a case of adult AMF, characterized by bone marrow panmyelopathy with marked megakaryocytic hyperplasia, increased blasts, and marked reticulin fibrosis, terminating in common ALL. Cytogenetic analysis of the bone marrow at the time of development of frank ALL revealed a terminal deletion of the short arm of chromosome 5 [del(5)(p15.3)]. This finding is not characteristic of ALL and supports the origin of the ALL from a stem cell disorder (i.e., AMF). Although various cytogenetic abnormalities, including trisomy 8, t(1;3),t(1;4), and occasional marker chromosomes, have been associated with AMF, there is no characteristic cytogenetic abnormality [13–16]. The most common chromosomal abnormalities in MDS are monosomy 5 or 5q−, monosomy 7 or 7q−, and monosomy 20 or 20q−; however, again there is no entirely specific pattern [17]; therefore, the distinction of AMF from MDS-F cannot be made based on the cytogenetic abnormality. Our case did not show typical morphological changes of MDS; the absence

of these changes virtually excludes the possibility of MDS-F [18].

The ALL was of the FAB L2 subtype and of early pre-B origin, as defined by flow cytometric immunophenotyping. Of interest, the lymphoblastic leukemia of early pre-B cell origin demonstrated expression of CD34, which is known to occur in 75% of cases and generally indicates a worse prognosis in adults [19]. However, an early pre-B immunophenotype and CD10 (Calla) positivity are good prognostic indicators [18]. Our patient was currently in complete remission 3 months after finishing maintenance therapy. All patients with follow-up reported to this time have died within 2 weeks to 2 months of diagnosis. Our case represents the only one in the literature with a complete remission.

As in other cases of AMF, the marrow fibrosis was most likely due to the megakaryocytic hyperplasia. In AMF, the myelofibrosis is most likely evoked by the megakaryocytic cell line, which produces and secretes transforming growth factor β. It stimulates collagen synthesis in bone marrow fibroblasts [20]. In addition, megakaryocytes also produce platelet mitogenetic factor, which stimulates proliferation of fibroblasts [20,21].

The association of AMF and ALL further supports the idea that AMF is a hemopoietic stem cell disorder that can terminate in blast crises of various origins. Thus, AMF may fall into the category of myeloproliferative disorders. There have been too few cases to determine the prognostic significance of termination of AMF in an acute leukemia of lymphoid origin vs. myeloid origin.

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